□ 5/3,AB/1 (Item 1 from file: 155)□DIALOG(R)File 155:MEDLINE(R)□(c) format only 2003 The Dialog Corp. All rts. reserv.□□11200395 98077013 PMID: 9415305□ The ' adenobody ' approach to viral targeting: specific and enhanced□adenoviral gene delivery.□ Watkins S J ; Mesyanzhinov V V; Kurochkina L P; Hawkins R E□ Bristol University, Department of Oncology, Bristol Oncology Centre, UK.□ Gene therapy (ENGLAND) Oct 1997, 4 (10) p1004-12, ISSN 0969-7128□Journal Code: 9421525□ Document type: Journal Article□ Languages: ENGLISH□ Main Citation Owner: NLM□ Record type: Completed□ Recombinant adenoviruses have enormous potential as vectors for gene□therapy. They have evolved an efficient method of infection and a wide host□range but this leads to concerns about the specificity of gene delivery. In□order to target an adenovirus type 5-based vector we have investigated an□antibody approach. A virus neutralising scFv antibody fragment was isolated□from a phage library and a C-terminal fusion protein with epidermal growth□factor (EGF) constructed. This fusion protein, or ' adenobody ', bound both□to the fibre protein of the adenovirus and to the EGF receptor (EGFR) on□human cells, and was able to direct adenoviral binding to the new receptor.□Using this system the efficiency of viral infection was markedly enhanced□and was targeted to the EGFR. The adenobody -directed infection correlated□with the level of EGF receptor expressed on the cells and could be blocked□by competition with pure EGF. Peptide inhibition experiments suggest that□infection is mediated directly through attachment to the EGFR and does not□require penton-integrin interactions. This work shows that the ' adenobody□' approach can enhance the efficiency as well as target adenoviral□infection and has numerous potential applications for gene therapy.□□□ 5/3,AB/2 (Item 1 from file: 159)□DIALOG(R)File 159:Cancerlit□(c) format only 2002 Dialog Corporation. All rts. reserv.□□ 02644329 20349401 PMID: 10889136□ Selective targeting of gene transfer to vascular endothelial cells by use□of peptides isolated by phage display.□ Nicklin S A; White S J; Watkins S J ; Hawkins R E; Baker A H□ Bristol Heart Institute, University of Bristol, UK.□ Circulation (UNITED STATES) Jul 11 2000, 102 (2) p231-7, ISSN□1524-4539 Journal Code: 0147763□ Document Type: Journal Article□ Languages: ENGLISH□ Main Citation Owner: NLM□ Record type: Completed□ BACKGROUND: Gene transfer to vascular cells is a highly inefficient and□nonselective process, defined by the lack of specific cell-surface□receptors for both nonviral and viral gene delivery vectors. METHODS AND□RESULTS: We used filamentous phage display to isolate a panel of peptides□that have the ability to bind selectively and efficiently to quiescent□human umbilical vein endothelial cells (HUVECs) with reduced or negligible□binding to nonendothelial cells, including vascular smooth muscle cells and□hepatocytes. By direct biopanning on HUVECs and a second approach involving□preclearing steps before panning on HUVECs, we isolated and sequenced 140□individual phages and identified 59 peptides. We selected 7

candidates for□further investigation by secondary screening of homogeneous phages on a□panel of cell types. Using adenovirus-mediated gene transfer as a model□gene delivery system, we cloned the peptide SIGYPLP and the positive□control peptide KKKKKKK upstream of the S11e single-chain Fv (" adenobody□") directed against the knob domain of the adenovirus to create fusion□proteins. Adenovirus-mediated gene transfer via fiber-dependent infection□was blocked with S11e, whereas inclusion of the KKKKKKK peptide retargeted□gene transfer. The peptide SIGYPLP, however, retargeted gene delivery□specifically to endothelial cells with a significantly enhanced efficiency□over nontargeted adenovirus and without transduction of nontarget cells.□CONCLUSIONS: Our study demonstrates the feasibility of using small, novel□peptides isolated via phage display to target gene delivery specifically□and efficiently to HUVECs and highlights their use for retargeting both□viral and nonviral gene transfer to vascular endothelial cells for future□ clinical applications.□?C

5/3,AB/1 (Item 1 from file: 155)
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The ' adenobody ' approach to viral targeting: specific and enhanced adenoviral gene delivery.
Watkins S J ; Mesyanzhinov V V; Kurochkina L P; Hawkins R E
Bristol University, Department of Oncology, Bristol Oncology Centre, UK.
Gene therapy (ENGLAND) Oct 1997, 4 (10) p1004-12, ISSN 0969-7128 Journal Code: 9421525
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
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DIALOG(R)File 159:Cancerlit

02644329 20349401 PMID: 10889136
Selective targeting of gene transfer to vascular endothelial cells by use of peptides isolated by phage display.
Nicklin S A; White S J; **Watkins S J** ; Hawkins R E; Baker A H
Bristol Heart Institute, University of Bristol, UK.
Circulation (UNITED STATES) Jul 11 2000, 102 (2) p231-7, ISSN 1524-4539 Journal Code: 0147763
Document Type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
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BACKGROUND: Gene transfer to vascular cells is a highly inefficient and nonselective process, defined by the lack of specific cell-surface receptors for both nonviral and viral gene delivery vectors. METHODS AND RESULTS: We used filamentous phage display to isolate a panel of peptides that have the ability to bind selectively and efficiently to quiescent human umbilical vein endothelial cells (HUVECs) with reduced or negligible binding to nonendothelial cells, including vascular smooth muscle cells and hepatocytes. By direct biopanning on HUVECs and a second approach involving preclearing steps before panning on HUVECs, we isolated and sequenced 140 individual phages and identified 59 peptides. We selected 7 candidates for further investigation by secondary screening of homogeneous phages on a panel of cell types. Using adenovirus-mediated gene transfer as a model gene delivery system, we cloned the peptide SIGYPLP and the positive control peptide KKKKKKK upstream of the S11e single-chain Fv (" **adenobody** ") directed against the knob domain of the adenovirus to create fusion proteins. Adenovirus-mediated gene transfer via fiber-dependent infection was blocked with S11e, whereas inclusion of the KKKKKKK peptide retargeted gene transfer. The peptide SIGYPLP, however, retargeted gene delivery specifically to endothelial cells with a significantly enhanced efficiency over nontargeted adenovirus and without transduction of nontarget cells.

CONCLUSIONS: Our study demonstrates the feasibility of using small, novel peptides isolated via phage display to target gene delivery specifically and efficiently to HUVECs and highlights their use for retargeting both viral and nonviral gene transfer to vascular endothelial cells for future clinical applications.
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